



Ultrasound-Detected Subclinical Synovitis and Flare Risk After Tapering Biologics in Rheumatoid Arthritis: A Review of the Evidence

Aditya Olsen^{1*}, Larissa Pavlovic², Latoya Dominguez³

¹Department of Medical Sciences, Siberian Center for Medical Sciences, New Zealand

²Department of Medical Sciences, Balkan Institute for Advanced Medical Sciences, Jamaica

³Department of Medical Sciences, Mekong Center for Medical Sciences, United Kingdom

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Abstract

Many people with rheumatoid arthritis now reach sustained clinical remission on a biologic agent, and the question of whether the dose can be reduced follows naturally. Tapering trials show that a substantial share of patients keep their remission on less drug, while others flare, and clinical features alone separate the two groups poorly. Musculoskeletal ultrasound detects synovial hypertrophy and power Doppler signal in joints that are neither tender nor swollen, and such subclinical synovitis has been proposed as the missing predictor. This narrative review examines the published evidence on that proposal. It summarises how remission and ultrasound synovitis are defined, what the tapering trials establish, and what cohort studies report on Doppler signal as a predictor of relapse after dose reduction or withdrawal of a biologic. It then considers why findings differ between studies and what the treat-to-target ultrasound trials imply. The literature supports a real but modest association between residual Doppler activity and later flare, with a notable negative study, and it does not show that scanning before tapering improves patient outcomes. Ultrasound is best regarded as one input to a shared decision and not as a gatekeeper.

Keywords: Rheumatoid arthritis, Musculoskeletal ultrasound, Subclinical synovitis, Power Doppler, Biologic tapering, Disease flare

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1. Introduction

Remission is now the stated goal of treatment in rheumatoid arthritis, and with biologic disease-modifying drugs it is reached by a proportion of patients that would have seemed improbable a generation ago. Success has created a new clinical problem. A person who has been well for a year or more on a tumour necrosis factor inhibitor or another biologic reasonably asks whether the same dose is still needed, and payers ask the same thing for different reasons. Current European recommendations state that tapering may be considered once remission is sustained and glucocorticoids have been stopped (Smolen et al., 2023). The American guideline is more guarded and conditionally favours continuing the

* Corresponding author: Aditya Olsen, Department of Medical Sciences, Siberian Center for Medical Sciences, New Zealand. E-mail: aditya.olsen@siberian.edu

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current dose, with dose reduction preferred to abrupt withdrawal when a change is made ([Fraenkel et al., 2021](#)).

Neither document tells the clinician which patient will flare. The usual clinical predictors, such as disease duration, depth of remission and autoantibody status, shift the odds without settling the matter ([Schett et al., 2016](#)). Ultrasound entered this discussion because of a consistent observation: many joints that look and feel normal in patients classified as in remission still show synovial thickening and vascular signal when scanned ([Brown et al., 2006](#)). If that residual inflammation is what drives relapse when treatment is reduced, a scan before tapering might identify the patients who should stay on full dose.

This article reviews what the published literature says about that idea. The focus is on biologic agents and on tapering, meaning dose reduction, interval spacing or withdrawal, in adults with established or early rheumatoid arthritis who have reached remission or low disease activity.

2. Scope and Approach

This is a narrative review of the published literature. It draws on the cohort studies, randomised trials, meta-analyses and consensus documents that are most often cited in this area and that the wider field treats as reference points. No formal search protocol was applied and no pooled estimate is offered. The aim is to set the main findings beside one another, to explain where they disagree, and to be explicit about what remains unproven. Studies of conventional synthetic drugs are included where they inform the question, since much of the early work on imaging in remission was done in patients on methotrexate.

3. Remission, Flare and the Ultrasound Lesion

Any claim that ultrasound predicts flare depends on three definitions, each of which is less settled than it first appears.

3.1. Clinical remission

Composite indices based on the 28-joint count were the first widely used remission definitions, and they allow a patient to be classed as in remission with several swollen joints. The joint definition issued by the American and European societies is stricter. Its Boolean form requires a tender joint count, swollen joint count, C-reactive protein in milligrams per decilitre and patient global assessment that are each no greater than one, and its index form requires a Simplified Disease Activity Index of 3.3 or less ([Felson et al., 2011](#)). Studies of tapering have used all of these definitions, and many enrolled patients in low disease activity instead of remission. The amount of residual synovitis to be expected on a scan differs accordingly.

3.2. Ultrasound synovitis and its scoring

The OMERACT ultrasound group defined synovial hypertrophy as abnormal hypoechoic intra-articular tissue that is non-displaceable and poorly compressible and that may show Doppler signal ([Wakefield et al., 2005](#)). Grey-scale imaging shows the tissue; power Doppler shows flow within it and is taken as the marker of active inflammation. A later EULAR-OMERACT taskforce combined the two into a single semi-quantitative grade from 0 to 3 for each joint ([D'Agostino et al., 2017](#)). Agreement between trained observers is generally acceptable for the small joints of the hands and feet, and reduced joint sets have been developed to make scanning feasible within a clinic appointment.

Two cautions apply. Low-grade grey-scale changes, especially in the metatarsophalangeal joints, are found in a fair number of healthy adults ([Padovano et al., 2016](#)), so grey-scale hypertrophy alone is a weak sign of disease. Doppler sensitivity also varies with the machine, the settings and the temperature of the hand, which makes thresholds hard to transfer from one centre to another.

3.3. Flare

There is no single accepted definition of flare. The OMERACT flare group described it as a cluster of symptoms of sufficient duration and intensity to require a change in therapy ([Bingham et al., 2009](#)), but individual studies have used a rise in the Disease Activity Score, loss of remission, the need to restart the biologic, or the physician's judgement. A prediction rule validated against one of these outcomes need not

hold for another.

4. What the Tapering Trials Establish

The trials of biologic tapering were not designed around imaging, but they set the background rate of failure against which any predictor has to work. Table 1 groups the main strands of evidence considered in this review. In the PRESERVE trial, patients with moderate disease who had reached low disease activity on etanercept and methotrexate did better if etanercept was continued at either the full or a reduced dose than if it was replaced by placebo (Smolen et al., 2013).

Table 1: Strands of evidence bearing on ultrasound and the tapering of biologics in rheumatoid arthritis			
Strand	Representative sources	Main message	Main limitation
Imaging in clinical remission	Brown et al., 2006; Saleem et al., 2011	Synovitis is often present in clinically quiet joints	Mostly conventional drugs; single centres
Doppler and relapse without tapering	Scirè et al., 2009; Foltz et al., 2012	Doppler signal is associated with later relapse	Flare definitions differ
Doppler and structural damage	Brown et al., 2008	Joints with Doppler signal are more likely to progress	Progression is small in absolute terms
Tapering trials	Smolen et al., 2013; Fautrel et al., 2016	Dose reduction succeeds in many, withdrawal in fewer	No imaging stratification
Ultrasound before tapering biologics	Naredo et al., 2015; Iwamoto et al., 2014	Baseline scores relate to failed tapering	Small cohorts, observational
Negative tapering cohort	Lamers-Karnebeek et al., 2017	Limited predictive value after stopping	Low disease activity, not strict remission
Ultrasound-targeted strategy trials	Dale et al., 2016; Haavardsholm et al., 2016	Targeting imaging remission adds no clinical gain	Not tapering trials

Strategy trials in established disease give a more cautious picture. In the Dutch DRESS study, stepwise dose reduction of adalimumab or etanercept guided by disease activity was non-inferior to usual care with respect to major flare, although short-lived flares were more common (van Herwaarden et al., 2015). The French STRASS trial of progressive injection spacing could not demonstrate equivalence with maintenance, and relapse was more frequent in the spacing arm, yet a good number of patients were able to reduce their exposure (Fautrel et al., 2016). After complete withdrawal of infliximab in the Japanese RRR study, roughly half of the patients kept low disease activity for a year (Tanaka et al., 2010).

Read together, these trials say that dose reduction is feasible for many patients, that complete withdrawal fails more often, and that most flares respond when the previous regimen is resumed. They also show how much room there is for a predictor: a test that reliably separated the half who will relapse from the half who will not would change practice.

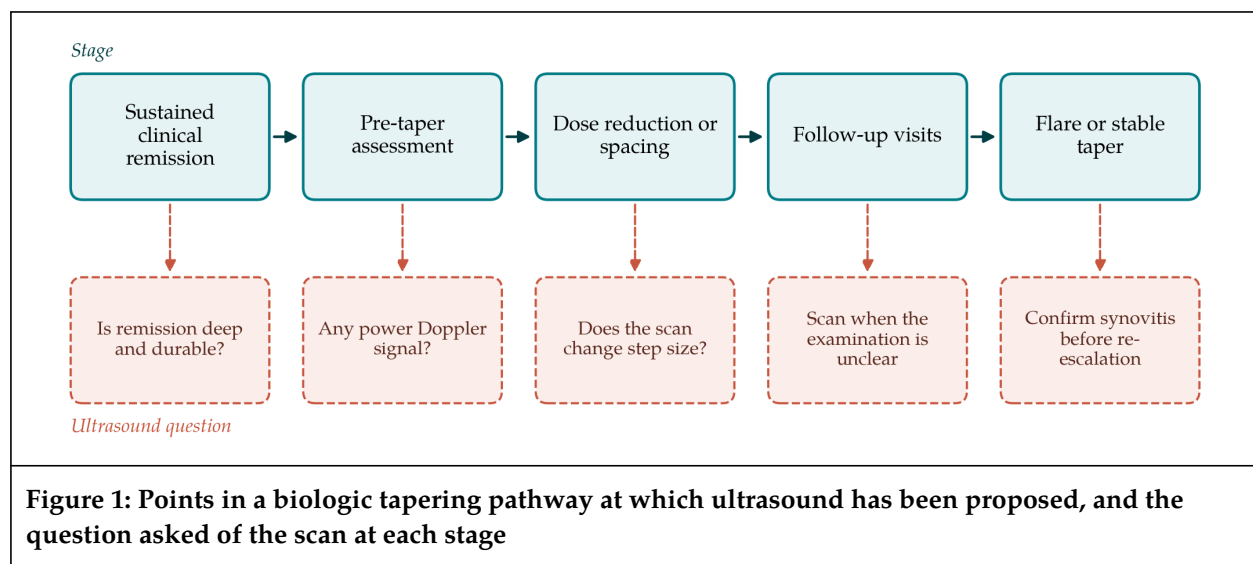
5. Subclinical Synovitis in Patients Who Are Not Tapering

The case for ultrasound was built first in patients whose treatment was left unchanged. In a cohort in clinical remission on conventional drugs, most patients had synovitis on ultrasound or magnetic resonance imaging despite normal examination (Brown et al., 2006), and joints with baseline power Doppler signal were the ones more likely to show radiographic progression over the following year (Brown et al., 2008). The same group showed that tightening the clinical definition of remission reduced but did not abolish imaging synovitis (Saleem et al., 2011) and that Doppler activity, together with functional disability, was associated with subsequent flare (Saleem et al., 2012).

Independent groups reported similar results. In early disease in clinical remission, a positive power Doppler signal identified patients at higher risk of relapse in the short term (Scirè *et al.*, 2009). Foltz *et al.* (2012) reported that power Doppler ultrasound, but not low-field magnetic resonance imaging, predicted both relapse and radiographic progression in patients with low disease activity. A meta-analysis of studies of this kind concluded that residual ultrasound synovitis is common in clinical remission and that Doppler signal is associated with a higher risk of relapse and of structural progression (Nguyen *et al.*, 2014). On this basis the EULAR imaging recommendations accept that ultrasound and magnetic resonance imaging can detect inflammation that predicts later damage even in clinical remission (Colebatch *et al.*, 2013).

6. Ultrasound Before Tapering a Biologic

Studies that scanned patients before a biologic was reduced are fewer and smaller. Figure 1 sets out the points in a tapering pathway at which a scan has been proposed and the question it is meant to answer at each. Naredo *et al.* (2015) followed patients in sustained remission whose biologic was tapered and found that Doppler-detected synovitis at baseline was associated with failure of the taper. Iwamoto *et al.* (2014) studied patients in clinical remission who stopped a biologic and reported that total grey-scale and power Doppler scores before discontinuation had high predictive value for relapse. Both studies were observational and modest in size, and in both the decision to taper had already been taken on clinical grounds.



The counterweight is a substudy of a Dutch trial of stopping tumour necrosis factor inhibitors in patients with low disease activity. There, ultrasound at the time of stopping had limited value in predicting flare over the following year (Lamers-Karnebeek *et al.*, 2017). The difference from the positive cohorts may lie in the population, since low disease activity admits more residual synovitis than strict remission and so leaves ultrasound less to discriminate. It may also lie in the intervention: abrupt withdrawal produces many flares whatever the baseline scan shows, and a predictor has less to add when the event is common.

What can be said with some confidence is limited. Residual Doppler signal before tapering is associated with a higher probability of relapse in most reports. The association is not strong enough to classify individual patients reliably: some with a clean scan flare and some with Doppler signal do not. And no study has yet shown that patients whose tapering decision was guided by ultrasound fared better than patients whose decision was made without it.

7. Why the Findings Differ

Several features of the literature explain its unevenness. The first is the scanning protocol. Studies have examined anything from a handful of joints to more than forty, and a reduced set may miss activity in the

feet or in large joints. The second is the threshold. Some studies treat any Doppler signal as positive, others require a grade of two or more, and total scores are summed in different ways. The third is the outcome, since flare has been defined by indices, by treatment change and by clinical opinion. The fourth is blinding. Where the treating physician knows the scan result, the decision to call a flare or to re-escalate may be influenced by it, which inflates the apparent predictive value.

Patient factors matter as well. Early disease treated promptly behaves differently from long-standing erosive disease, in which grey-scale thickening may reflect inactive pannus or secondary osteoarthritis. The class of biologic and the continuation of methotrexate alter relapse rates independently of imaging. Few studies were large enough to adjust for these influences, and publication of small positive cohorts ahead of small negative ones cannot be excluded.

8. Lessons From the Ultrasound Strategy Trials

Two randomised trials tested whether aiming for imaging remission improves outcomes in early disease. In the Scottish TaSER trial, a strategy that escalated treatment on the basis of power Doppler findings led to more intensive therapy without a significant improvement in clinical or imaging outcomes compared with a strategy driven by the Disease Activity Score ([Dale *et al.*, 2016](#)). The Norwegian ARCTIC trial reached the same conclusion for an ultrasound-informed tight control strategy against conventional tight control ([Haavardsholm *et al.*, 2016](#)).

These were not tapering trials, and their results should not be stretched too far. They do establish a principle that bears on the present question. A marker can be associated with a poor outcome and still fail to improve care when it is used to steer treatment, because acting on it brings costs of its own. For tapering, the corresponding cost is that patients with harmless residual signal would be kept on full-dose biologic indefinitely.

9. Gaps and Future Work

The decisive study has not been done. It would randomise patients in sustained remission to tapering guided by clinical assessment alone or by clinical assessment plus a standardised scan, with flare, function, radiographic progression and drug exposure as outcomes and with assessors unaware of the imaging. Short of that, prospective cohorts could adopt the EULAR-OMERACT scoring system and a common flare definition so that their results can be combined. Reduced joint sets need to be tested specifically for prediction after tapering, since their original validation concerned responsiveness to treatment.

Other questions are open. Little is known about ultrasound prediction with non-TNF biologics or with targeted synthetic drugs, about the value of repeating the scan during a taper, or about how imaging compares with serological and other laboratory predictors when they are used together. Cost matters too: a scan performed by a rheumatologist takes clinic time, and any saving from reduced drug use has to be set against it.

10. Conclusion

Subclinical synovitis on ultrasound is common in rheumatoid arthritis patients who appear to be in remission, and persistent power Doppler signal is associated with later relapse and with structural progression. In the smaller literature on tapering biologics, baseline Doppler activity has usually, though not always, been linked with failure of the taper. The evidence does not yet show that scanning before tapering leads to better results for patients, and the strategy trials in early disease counsel against assuming that it will. For the present, an ultrasound examination is a reasonable aid when the clinical picture is uncertain, and its findings belong alongside disease duration, depth and length of remission, serology and the patient's own preferences in a shared decision about dose.

Conflict of interest

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